Engineering Embryonic Stem Cell Allografts for Operational Tolerance

Grant Award Details

Engineering Embryonic Stem Cell Allografts for Operational Tolerance

Grant Type: Transplantation Immunology

Grant Number: RM1-01706

Project Objective: The project objective is to protect ES and iPS cells, and their derivatives, from allograft rejection by genetic modification. The objective is to test set of immunomodulatory genes in ES to reduce allograft rejection.

Investigator:

Name:	Christopher Contag
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: Adult Stem Cell, iPS Cell

Cell Line Generation: Adult Stem Cell, iPS Cell

Award Value: $1,411,338

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3 + NCE

View Report

Grant Application Details

Application Title: Engineering Embryonic Stem Cell Allografts for Operational Tolerance

Public Abstract: Stem cells, like all transplants not derived from an identical twin, are subject to scrutiny by the immune system and, without medical interventions that suppress the immune system, are usually killed after transplantation. However, rare exceptions to this rule exist because a small fraction of transplant patients has been able to maintain their transplant in the absence of immunosuppressive drug therapy and developed "operational tolerance" towards the foreign graft. Our team has extensively studied these patients and identified a number of genes that are characteristically overexpressed or silenced in these patients. Other instances of tolerance towards foreign cells also occur naturally, e.g. during pregnancy. While numerous genes that correlate with operational tolerance are known, it is less clear whether they actively contribute to tolerance and how they compare in their effectiveness. We will therefore transfer this collection of genes, one-by-one or as combinations, into mouse embryonic stem cells using gene therapy methods and identify those genes that can best protect the cells from rejection by the immune system.

To accurately monitor the survival of transplanted stem cells in mice over time we will use in vivo bioluminescence imaging (BLI). For this, we label the stem cells with luciferase, a protein from the firefly that emits light. These bioluminescent stem cells are transplanted into recipient mice (whose background luminescence is negligible) where the cells can be repeatedly and non-invasively visualized with a highly sensitive camera system. Thus, the cellular survival, growth and migration can be assessed over time and under various conditions, and we can determine whether the introduced genes affect the survival of stem cell transplants positively or negatively, and how they compare and, hopefully, cooperate.

Our preliminary data show that we can detect differences in survival of such engineered cells. This indicates that the proposed studies will succeed in prolonging the survival of mouse stem cell transplants, and that these studies are greatly accelerated by the use of BLI and of gene transfer methods developed over the past several years in our and other laboratories. The potential impact of this proposal is substantial, in that successful completion of the specific aims will both be an important step towards tissue replacement and regeneration using stem cells, and the first demonstration of a multiplexed gene screen in mice. If the genes found to modulate the immune system locally and to protect stem cell transplants in mice can be translated to the bedside, e.g. developed into small molecule drugs that are safe to administer, there is promise that we can reduce the untoward effects of systemically delivered drugs, and extend the lifespan of stem cell and organ transplants without the need for chronic immunosuppression. This would have a substantial impact of the management of a variety of medical conditions.

Statement of Benefit to California:

The California Institute of Regenerative Medicine is seeking to discover new therapeutic approaches that use stem cells for a wide range of diseases and to critically evaluate these for the citizens of California. Unfortunately, however, transplanted stem cells derived from genetically unrelated donors are recognized as foreign by the recipient's immune system and usually destroyed within a month. Currently, the only treatment option for stem cell and organ transplants consists of immunosuppressive drug therapy that is costly and due to its systemic and nonspecific effects carries substantial risks of infection and cancer.

Tolerance to foreign tissues, nevertheless, can develop naturally, for example in women during pregnancy where the partially mismatched fetus is tolerated, and in rare patients who are fortunate enough to maintain their mismatched grafts in the absence of immunosuppressive drug therapy. It is from these instances, which our group has studied extensively, that we will take our clues to develop a comprehensive understanding of transplant tolerance and its genetic basis. Because without this and without an effective means of transferring this tolerance to stem cells, the tremendous potential of the new stem cell therapies may not be realized. Even autologous stem cell therapies, in which patients receive induced pluripotent stem cells (iPSCs), which are derived from their own cells and therefore not mismatched, if they were to succeed otherwise, will not benefit patients with autoimmune disorders, like type 1 diabetes, who will still react to and destroy any transplanted tissue. Therefore, alternatives that modulate the immune response at the site of the engrafted cells or tissues are clearly needed.

Our plan is to select out of the mouse genome the quintessential set of genes whose up- or down-regulation is necessary and sufficient for the long-term protection of stem cell transplants in genetically mismatched mice. In this innovative and comprehensive genetic approach, we will modify the expression of individual genes or groups of genes in mouse stem cells, and observe the cells' fate after transplantation with powerful imaging technologies that are non-invasive and highly sensitive. Thus, the effect of each gene on the survival of a stem cell transplant can be easily measured and comparatively evaluated, as well as each gene be examined for cooperativity with other genes in the induction of tolerance.

Acquiring this genetic knowledge and translating it into effective stem cell therapies for human patients will be the critical steps in a continuum of research that will clearly benefit citizens in California and elsewhere. Because making stem cell transplantation more efficient and better tolerated will not only advance the fields of stem cell biology and medicine but also that of organ transplantation in general so that less suffering and costs will be incurred in the future in terms of lost lives and funds.
